AF/1625
#2 mail

PTO/SB/21 (08-03)
Approved for use through 08/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/702,944
Filing Date	October 31, 2000
First Named Inventor	Fukuda
Art Unit	1625
Examiner Name	P. Morris
Attorney Docket Number	104610-49984 (20498)

Total Number of Pages in This Submission: 33

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Postcard; Appendix A (5 pages).

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	William H. Epstein; Registration No.: 20,008 Gibbons, Del Deo, Dolan, Griffinger & Vecchione
Signature	
Date	April 17, 2004

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Tracie Hibbits		
Signature	Tracie Hibbits	Date	4-8-04

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 165.00

Complete if Known	
Application Number	09/702,944
Filing Date	October 31, 2000
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METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 03-3839

Deposit Account Name: Gibbons, Del Deo, Dolan

The Director is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X =
Independent Claims		- 3** =		X =
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	165.00
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 165.00

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	William H. Epstein	*Registration No. (Attorney/Agent)*	20,008	*Telephone*	973-596-4500
Signature	William H. Epstein			*Date*	4/7/04

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Tracie Hillerts 4-8-04
(Signature and Date)

PATENT
104610-49984 (20498)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Patent Application of: Fukuda et al.			Art Unit : 1625
Serial No.	:	09/702,944	Examiner : P. Morris
Filed	:	October 31, 2000	
Title	:	N-SUBSTITUTED CARBAMOYLOXYALKYL-AZOLIUM DERIVATIVES	

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Dear Sir:

This is an appeal under 35 U.S.C. §134 from the final rejection of October 30, 2003 of claims 1-9, 15-18, 22, 23, 26, 27, 30 and 31 of the captioned application. This brief is in support of the Notice of Appeal filed February 20, 2004.

I. STATEMENT OF REAL PARTY INTEREST

The real party of interest in this appeal is the assignee of record, Basilea Pharmaceutica, AG, a corporation of Switzerland, having offices at 11 Neuhoag, CH-4102, Binnigen, Switzerland.

II. STATEMENT OF RELATED APPEALS AND INTERFERENCES

There are no other related appeals or interferences.

III. STATUS OF THE CLAIMS

Nineteen claims, claims 1-9, 15-18, 22, 23, 26, 27, 30 and 31, all of the claims pending in the captioned application, stand finally rejected and are presented here on appeal. A copy of these appealed claims is attached as Appendix A.

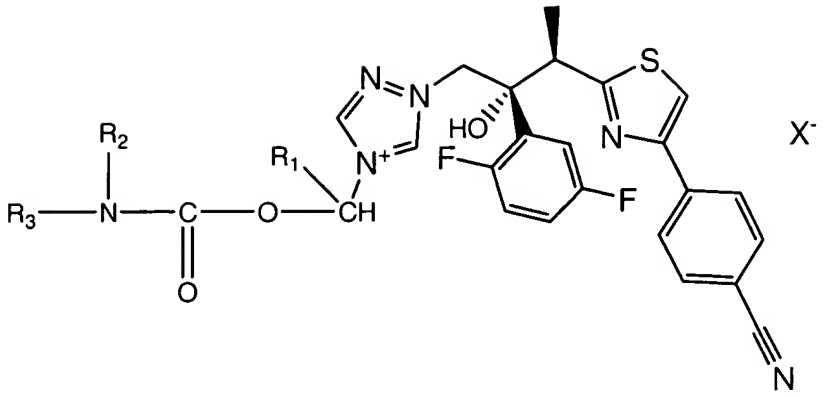
IV. STATUS OF AMENDMENTS AND PRIOR HISTORY

Claims 1-9, 15-18, 22, 23, 26, 27, 30 and 31 stand finally rejected in the Office Action dated October 30, 2003. No amendments to the claims were made after this final rejection.

V. SUMMARY OF INVENTION

This invention is directed to the compounds of the formula

I



R_1 is hydrogen or alkyl;

R_2 is hydrogen, alkyl, alkylcarbonyloxyalkyl, alkoxycarbonyl, alkylcarbonyl, mono- or dialkylaminoalkylcarbonyloxyalkyl;

R_3 is pyridin-2-yl or substituted pyridin-2-yl; and

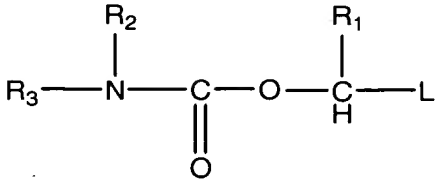
X^- is a pharmaceutically acceptable anion, and when R_3 is substituted pyridin-2-yl, the substituent is selected from the group consisting of halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkyloxycarbonyl, cyano, trifluoromethyl, trifluoromethoxy, nitro, aminosulfonyl, alkylaminocarboyloxyalkyl, sulfo, alkylcarbonyloxyalkyl and aminoalkylcarbonyloxyalkyl;

or a pharmaceutically acceptable salt thereof.

As set forth on page 1, lines 5-7, these compounds of formula I are useful as antifungal agents and as such are used in treating mycosis. The antifungal agent of the compound of formula I are disclosed on page 73, lines 4 thorough 10 as being useful in treating fungal infections such as systemic candidiasis, systemic aspergillosis and pulmonary aspergillosis.

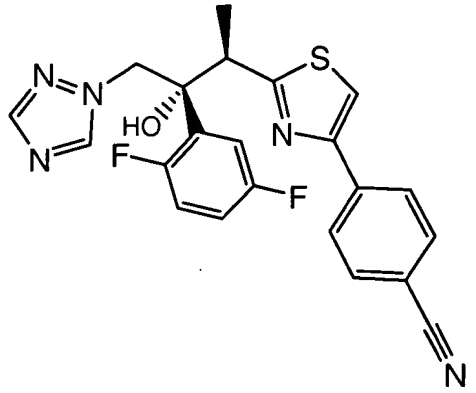
The compound of formula I can be formed, in accordance with disclosure in the captioned application, on page 18, lines 19-25 and the schemes on pages 29 and 30, by reacting an intermediate of the formula

IV



wherein R_1, R_2 and R_3 are as above and L is a leaving group with a triazole of the formula:

V



VI. REFERENCES

The three references used to reject the claims are:

1. Hayase et al., U.S. Patent 6,300,353, issued October 9, 2001;

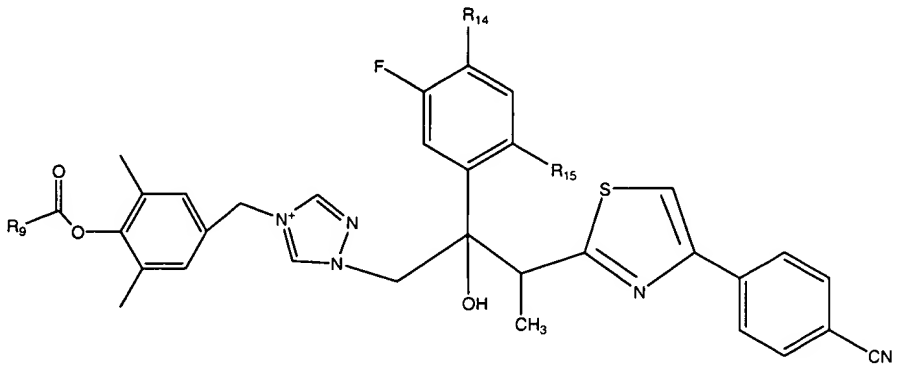
2. Hudayma, U.S. Patent 6,265,584, issued July 24, 2001; and

3. Davidsen et al., *J. Med. Chem.*, **37(26)**: 4423-4429 (December 23, 1994).

VII. DISCUSSION OF REFERENCES

Hayase et al., U.S. Patent 6,300,353, disclose, in column 3, lines 20-35, the aforementioned triazole of formula V as useful as a drug for treating fungal infections. This triazole of formula V is named in column 5, lines 5 and 6 as (2R, 3R)-3-4-[4-cyanophenyl)thiazol-2-yl]-2-[2,5-difluorophenyl]-1-(1H-1,2,9-triazol-yl)-butane-2-ol. This triazole is disclosed, in column 3, lines 1-20, as a chemical intermediate for fungicide of the formula:

VIII

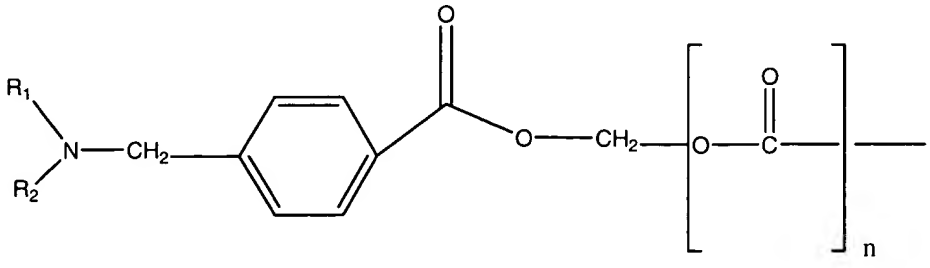


wherein R_{14} and R_{15} are independently hydrogen or fluorine;
R_9 is pyrrolidinyl or a group A-NH-B;
A is hydrogen or alkyl
B is alkylene, etc.

Hudyama, U.S. Patent 2,265,589, in column 2, lines 30-35, discloses the butane-2-ol triazole of formula V as an antifungal compound. In accordance with Hudyama's

disclosure this triazole of formula V above is used to produce an antifungal compound by coupling, through the 2-ol group of the butane-2-ol, a moiety of the formula:

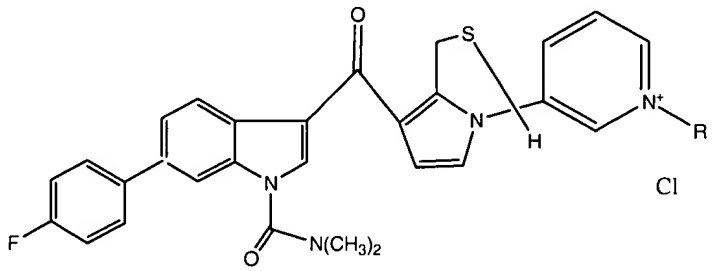
X



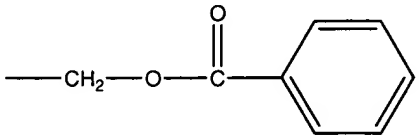
wherein n is 0 of 1, R_1 and R_2 taken together with their nitrogen form a non aromatic heterocyclic ring. None of the heterocyclic rings formed by R_1 and R_2 disclosed by Hudyama are other than non aromatic saturated rings. See Column 1, lines 37-48.

Davidsen, *J. Med. Chem.*, **37(26)**:4423-4429 (December 23, 1994), discloses specific pyridinium salts of the corresponding pyridine compound **4**:

XI



where, among other things, R which forms the salt is



The different salts corresponding to given R group are listed in Table 1 on page 425. Davidsen also discloses in Table 1 that these salts are stable salts of the corresponding

pyridine compounds (the compounds where R is removed). In Table 1 Davidsen also gives the half-life of those pyridinium salts for their conversion into the corresponding pyridine compound 4 in human plasma. The plasma half-lifes vary from 1 minute up to 160 minutes depending on the structure of R. Compound 16 is practically not cleaved (plasma half-life > 600 minutes. Davidsen states on page 424, column 2, lines 37-45 that " The pyridinium salts listed in Table 1 are completely soluble in pH 3 aqueous buffer" Also Davidsen discloses that these compounds are useful for treatment of inflammatory disorders, septic shock and asthma.

VIII. UMEDA DECLARATION

Applicants have filed, on July 24, 2004, a Declaration by Isao Umeda, pursuant to 37 C.F.R. §1.132, to demonstrate that different compounds derived from the triazole of formula V have a different therapeutic value. In this respect, the compound of Example 1 of the Hayase patent prepared from the triazole of formula V was tested against a compound of this invention also prepared from the triazole of formula V. The compound of this invention which was tested is disclosed in Example c on page 66 of this application. This compound is a pyridine carbamoyloxyalkyl-azolium prepared from the triazole of formula V.

As seen from the results reported in this Declaration the antigenicity of a pyridine carbamoyloxyalkyl-azolium prepared from the triazole of formula V, as claimed in the present invention was negative. On the other hand the antigenicity of the corresponding compound prepared from the triazole of formula V disclosed in Example 1 of the Hayase et al. patent is positive

In this antigenicity study, a series of tests were conducted in guinea pigs, in particular, active systemic anaphylaxis (ASA) tests and passive cutaneous anaphylaxis (PCA) tests were performed. Specifically, the antigenicity studies were performed on Hayase et al. (compound j from example 1 in Column 19) and applicants' compound

(compound 2, example c on page 66 of applicants' specification). No positive ASA reaction or PCA reaction was observed in animals immunized with 30 mg/animal of compound 2 plus Freund's adjuvant (FA) and challenged with 1 mg/animal of compound 2 alone or with 1 mg/animal of compound 2-ovalbumin (OVA) mixture. No positive ASA reaction or PCA reaction was observed in animals immunized with 3 mg/animal of compound 2 guinea pig serum albumin (GPSA) mixture plus FA and challenged with 1 mg/animal of compound 2 alone or 1 mg/animal of compound 2-OVA mixture. The results from this study show that the antigenicity of applicants' compound 2 was negative. Active systemic anaphylaxis (ASA) tests on the prior art compound of Hayase et al., compound 1, on the other hand, demonstrated that the antigenicity of compound 1 was positive.

This demonstrates that the compound which includes the compound of formula V tested by Umeda which is in accordance with this invention is a less toxic compound having a higher therapeutic value than the fungicides of Hayase which also includes the compound of formula V in their structure. Based upon the results in this declaration, the compounds prepared from the triazole of compound V in accordance with this invention have different therapeutic value than compounds prepared from the triazole of Formula V in accordance with the disclosure of the Hayase patent.

IX. THE REJECTIONS

All of the claims have been rejected under 35 U.S.C. §102, as being anticipated by the Hayase et al. Patent. The basis for this rejection, as stated in the Office Action of March 5, 2002 (Paper No. 7), is that "Itoh et al.[1] specifically recite the compound. (Note Column 5, line 6). As stated on page 3 of this Office Action, this conclusion that the final claimed product is anticipated by the precursor disclosed in Hayase is based on the grounds that:

[1] In this rejection Itoh et al. is miscited and should be the Hayase et al. patent.

> "The precursor and final product are not different products, regardless of differences in their activity and efficacy. See Marian Merrell Dow Inc. v. American Cyanamide Co., 36 USPQ 7 1036. Hence the instant compound is deemed to be anticipated therefrom."

In this regard, in the Final Office Action (Paper No. 26) of October 30, 2003, the Examiner states:

> "Applicants assert that the fact that Applicants' compounds may be enzymatically cleaved to the body generate the parent compound does not make the compounds the same as the parent compounds. They are in fact the **same** compounds. Applicants have **failed** to provide any objective evidence that the compounds are, in fact, not the same. Attorneys arguments do not take the place of objective evidence."

The claims have also been rejected under 35 U.S.C. §103 over Hayase et al. in view of Hudyama et al. and Davidsen. As stated on page 4 Of the Office Action of March 5, 2002 these references are cited for the fact that:

> "Hayase et al. disclose the final product having the same use. Note compound 43 therein[2]. Hudyama teaches that analgous amine salts similar to those of the claimed invention retained the activity associated with the final products, whereas Davidsen teaches that pyrridine salts are known to be extremely soluble."

As the basis for this rejection, the Examiner stated on page 4 of this Office Action:

> "It is well settled that the final product and precursor are not different products, regardless of differences in their activity and efficacy. Marian Merrell Dow Inc. v. American Cyanamide, *supra*."

The Declaration of Dr. Umeda, in the Final Office Action is held to be of little probative value because it fails to include the final product and the elected compound. In addition, this Declaration is not considered to be probative since the claims are directed to using the instant compounds for the treatment of fungal infections, whereas the Declaration is not directed to treating fungal infections. Furthermore, the Examiner

[2] Applicants have been unable to find compound 43 in the Hayase et al. patent.

holds that the Declaration is not in commensurate scope with the claims and that it demonstrates no unexpected or unobvious results.

Claims 3 and 4 have been rejected under 35 U.S.C. §112, first paragraph, in view of the use of the term "hydrolizable acyl." In this rejection, it is alleged that this term is not described and one skilled in the art would not be enabled to make or use the invention in accordance with the scope claimed in claims 3 and 4.

X. ISSUES

1. Whether claims 1-9, 15-18, 22, 23, 26, 27, 30 and 31 are anticipated under 35 U.S.C. §102(b) by the Hayase et al. patent;

2. Whether claims 1-9, 15-18, 22, 23, 26, 27, 30 and 31 are unpatentable as being obvious over Hayase et al. in view of Hudyama et al. and Davidsen et al.; and

3. Whether the term "hydrolizable aryl groups in claims 3 and 4 is described or enabled by the specification as required by 35 U.S.C. §112, first paragraph.

XI. GROUPING OF THE CLAIMS

With respect to the rejections under 35 U.S.C. 102(b) and 35 U.S.C. §103, all of the claims should be grouped together since they all cover the specific elected species. With respect to the 35 U.S.C. §112, first paragraph, rejection, only claims 3 and 4 are involved. Therefore, claims 1-2, 5-9, 15, 18, 22, 23, 26, 27 30 and 31 should not be effected by this rejection.

XII. ARGUMENTS

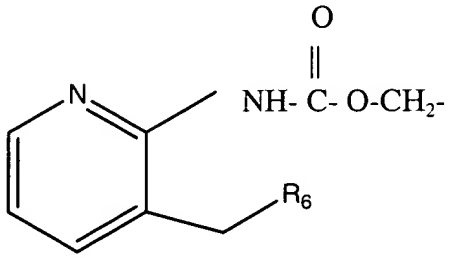
A. The Hayase Patent Does Not Anticipate the Claimed Invention

1. The Hayase Patent does not ever disclose Applicants claimed compounds.

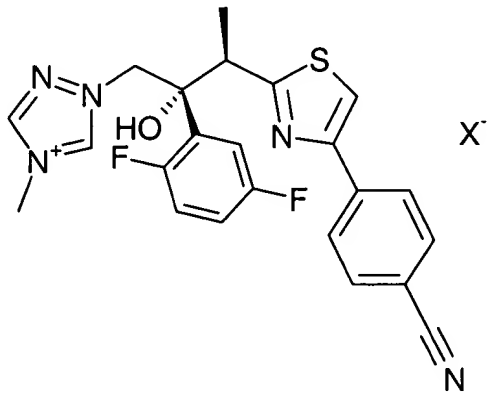
At the outset Applicants wish to point out that the claimed compounds are formed with the following two parts:

A — B

In its simplest terms, Part A is a pyridine carbamoyloxyalkyl-moiety of the formula:



and Part B is an triazole moiety of the formula:



As seen above, Part A is connected to Part B by a nitrogen in the triazole of Part B

Hayase discloses Part B as a compound used as an intermediate for other compounds. However the claimed compound is not Part B. It is Part A connected to Part B by means of the carbamoyloxyalkyl linkage to a nitrogen in the triazole ring of Part B. In order for there to be anticipation, under 35 U.S.C. 102, all of the elements of the claim must be present in the prior art. Without this, a rejection under 35 U.S.C. 102 is not proper. This is clear from the decision of the CCPA in In re Marshal, 198 USPQ

344, which reversed a rejection based on anticipation. In reversing this rejection, the CCPA, at page 346, stated

> Rejections under 35 U.S.C. 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art. In re Arkley 59 CCPA 804... 172 USPQ 524, 526 (1972). In other words, to constitute anticipation, all material elements recited in a claim must be found in one unit of the prior art... This basic principal of Patent Law has not been disturbed...

Hayase does not identically disclose or describe the claimed compounds of this invention as required for a 35 U.S.C. 102 anticipation rejection. Since the Hayase reference fails to teach Part A of the claimed compound, it does not set forth all of the elements of the claimed compound. Therefore a rejection under 35 U.S.C. 102 is not proper.

Attention is also direct to In re Meyer, 202 U.S.P.Q. 175, where the CCPA held that even the disclosure of a genus by the prior art does not constitute anticipation under 35 U.S.C. 112, even though the claim species is embodied within the genus. As stated by the CCPA in In re Meyer, 202 USPQ 175 at 179, in holding that the genus does not anticipate the species.

> "For Reissert (the Prior art) to constitute an anticipation, it must identically disclose or describe, inter alia, reacting an alkali metal salt of . . . with an alkali metal hypochlorite. . . . The genus, "alkaline chlorine or bromine solution," does not identically disclose or describe, within the meaning of §102, the species alkali metal hypochlorite."

Hayase is even more remote than the Reissert reference used in In re Meyer supra, since it does not cover or describe the claimed subject matter, even generically, much less identically as required for a 35 U.S.C. 102 rejection.

2. Final Products Are Not The Same Compounds As Intermediates Despite Similarities In Their Activites

In the Final Rejection it is stated on page 3 that:

> "The precursor and final product are not different products regardless of differences in their activity and efficacy."

It is clear that they are different products since their structures are completely different. That the claimed compound incorporates the triazole precursor disclosed in Hayase et al. as Part B within its structure does not make it the same compound. There is no disclosure in Hayase of the pyridine carbamoyloxyalkyl-moiety set forth in Part A, much less attached to this triazole. In fact, Hayase does not disclose a pyridine ring or a carbamoyloxyalkyl-moiety. What is attached to the triazole group of Part B in the Hayase compount via a methylene bridge is a dimethyl substituted phenyl group. No such dimethyl phenyl bridge exists in the claimed compounds of this invention. Clearly these compounds are structurally different. That they contain the same fungicidal drug (part B) does not make them the same compound in respect to their therapeutic value, especially in respect to toxic side-effects.

In addition, on page 3 of the Final Office Action, it is stated that:

> "Applicants assert that the fact that Applicants' compounds may be enzymatically cleaved in the body to generate the parent compound does not make the compounds the same as the parent compounds."

If anything, this assertion that the compounds of this invention may be enzymatically cleaved in the body is taught by applicant and not the prior art. The fact that the compound of this invention may be enzymatically cleaved in the body to the precursor does not make the precursor and final product the same compound. They are not. It is the Examiner that has the burden of establishing by the objective evidence that the compounds are in fact the same. Their different structures present the objective evidence necessary to establish that they are different compounds. No basis exists for the assertion that precursor and the claimed compounds are the same compound.

3. The Marian Merrell Dow Decision Provides No Basis For Asserting That The Claimed Compound And The Precursor Are The Same Compound

In order to rely upon Hayase being an anticipation of the claimed invention, Marian Merrell Dow Inc. v. American Cyanamide, 36 USPQ 2nd 1036, is cited This decision has nothing to do with whether the fact that the claimed compound, which consists of Part A and B, is enzymatically cleaved in the body to the compound of Part B, disclosed by the prior art, is sufficient to establish anticipation. This decision has nothing to do with asserting that the claimed compound and its enzymatically cleaved precursor are the same compounds. The question of anticipation is a question of patentability. The issue presented in the Marion Merrell Dow, *supra*, involved an issue of infringement. The issue in the Marion Merrell Dow case was whether the importation of a product produced abroad by a process patented in the US infringed, under the US, the Process Protection Act, when the product imported was further processed abroad. The court in the Marion Merrell Dow case held that in view of the evidence, the further processing of the product abroad was a trivial step and did not materially change the product produced by the patented process. In view of this, the court held that the importation of this further processed product constituted an infringement under the Process Protection Act.

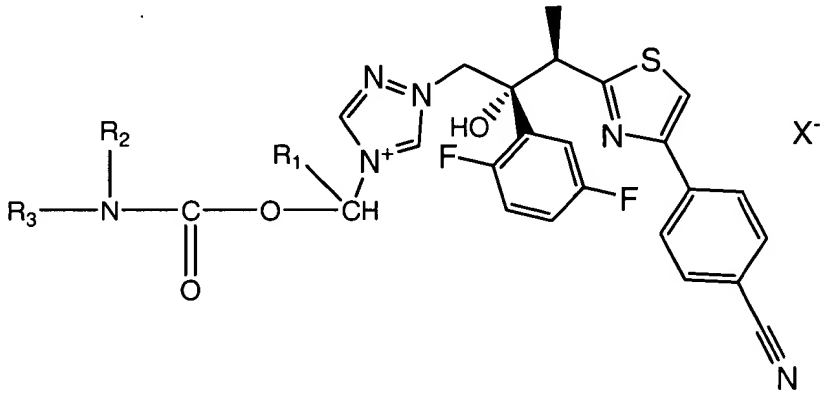
Issues of patentability and infringement are totally different. Whether a product which falls under the Process Protection Act so as to infringe a US process patent is no way related to the patentability of that product. It is well settled that inventions although embraced within a generic claim of the prior art and which infringed this generic claim can be patentability distinct from the claimed generic invention. See Hester v. Allgeier, 209 USPQ 370 (CCPA 1981). In addition, see the In re Meyer, decision, supra, discussed above, which held that the term alkaline chloride used by the prior art covered the claimed alkaline metal hypochloride, its disclosure did not anticipate or even render obvious the claimed invention Clearly issues of patentability and infringement are two different issues.

Furthermore, in the Merrell case, supra, in order to hold that acetylation step did not materially change the product produced by the claimed process, the court, on page 1040, relied upon evidence which included various affidavits, various declarations and deposition testimony of three Ph.D's. On the other hand the instant office action provides no evidence for the statement that the precursor and final product are the same product. Without the evidence in the Merrell case, supra, the court could not have reached their conclusion concerning the fact that the step of acetylation did not materially affect the product of the claimed process. However while this evidence may be pertinent to an issue of infringement, it has no pertinence to an issue of patentability

B. The Hayase Patent Taken Together With Hudyama and Davidsen Does Not RenderObvious the Claimed Invention.

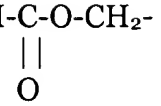
1. None of the References Disclose The Claimed Structure

The claimed compound, in its simplest form, formed by attaching Parts A to the nitrogen of the triazole ring of Part B has the following formula:

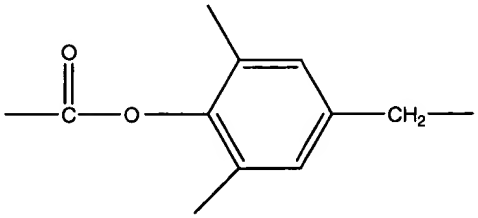


wherein R_1, R_2 are hydrogen and R_3 is a pyridinyl ring.

In this case, a pyridinyl ring is connected to the triazole of Part B through a carbamoyloxyalkyl bridge of the formula:



This bridge is not disclosed by Hayase in the final products made from the triazole. As seen from formula I in column 1, lines 20-39, the bridge is



which is totally structurally different from the carbamate bridge of this invention. There is no disclosure in Hayase of any pyridine carbamoyloxyalkyl-moiety such is set forth in Part A much less attached to this triazole. What is attached to the triazole group of Part B in Hayase via a methylene bridge is a dimethyl substituted phenyl bridge. No such dimethyl phenyl bridge exists in the claimed compounds of this invention.

In addition there is no disclosure in Hayase of pyridinyl at the other end of this dimethyl substituted phenyl bridge. Pyrrolidinyl which is at the other end of dimethyl substituted phenyl bridge is not pyridinyl. While pyrrolidinyl and pyridinyl are heterocyclic moieties, pyridinyl is an aromatic heteroaromatic moiety, whereas pyrrolidinyl is a saturated non-aromatic heterocyclic moiety. In addition, pyridinyl is a 6 membered ring, whereas pyrrolidinyl is a 5 membered ring. Clearly, these are different moieties. This coupled together with the different bridges produces compounds having totally different structures except for the presence of the triazole of Part B within the structure. Furthermore, this dissimilarity in structures does not give rise to any presumption of obviousness.

The Davidsen and Hudyama references do not remedy the defects in the Hayase disclosure. Hudyama has the same type of bridge, as Hayase, attached to a non-

aromatic heterocyclic moiety, not pyridine. The heterocyclic moieties of Hudyama are all saturated rings and not heteroaromatic moieties like pyridine. What was said about Hayase can also be applied to Hudayma. Like Hayase, there is no disclosure in Hudayma of any pyridine carbamoyloxyalkyl-moiety such as set forth in Part A, much less attached to this triazole. Hudayama, links the heterocyclic radical to the triazole group of Part B by means of an ester or polyester structure interrupted by a phenyl radical. This phenly radical is not present in the bridge of Part A of the compound of the invention. Also in Hudyama, the tertiary hydroxy group of the butan-1-ol of the triazole of Part B is linked by the bridge to the non-aromatic heterocyclic ring. There is no disclosure in Hudyama of forming this bridge on the nitrogen of the triazole moiety as in the claimed compounds of this invention. Clearly, Hudyama adds very little to the disclosure in Hayase.

Davidsen is cited as disclosing the use of pyridine moiety to solubilize compounds. Davidsen does not disclose that the presence of pyridine solublizes compounds. Davidsen discloses that the solubility of certain pyridine containing compounds may be improved by forming certain specific salts. Davidsen compounds are in no way related to the compounds of this invention except that they contain a pyridine moiety within their structure. Unlike Hayase or Hudayma, the compounds of Davidsen contain no triazole of Part B within its structure. Davidsen's compounds are entirely different than the compounds of this invention or the compounds of Hayase or Hudayma. The compounds of Davidsen are used for an entirely different purpose than the compounds of this invention. They are not disclosed as being fungicides but rather disclosed as being useful for the treatment of inflammation, septic shock and asthma. There is no teaching by Davidsen of utilizing pyridine or even salts of pyridine in molecules other than that disclose in their Table 1.

2. Even By Combining The References One Would Not Obtain The Claimed Compounds

Even if one were to combine Hayase with Hudyama, one would still not obtain the claimed compound of this invention having the triazole of Part B connected to a pyridine moiety by a carbamoyloxyalkyl bridge to a nitrogen in the triazole ring of Part B. This is true since there is no disclosure in either of these references of any pyridine ring moiety. None of these references disclose a carbamoyloxyalkyl moiety. What is attached to the triazole of Part B in the Hayase compound bridge is a dimethyl substituted phenyl ring. Hudyama links the non-aromatic heterocyclic group to the triazole group of Part B by use of an ester or polyester structure interrupted by a phenylene moiety. Also in the Hudyama compound, the tertiary hydroxyl group of the butane-1-ol of the triazole of Part B is linked to the non-aromatic heterocyclic ring through a phenyl ring. One could not construct, even if Hudyama or Hayase disclosed pyrridyl in place of their non-aromatic heterocyclic ring, the claimed structure of the compounds of this invention based upon the disclosure of Hudyama and Hayase. In no way can this combination, even forgetting the lack of a disclosure of pyridine, form the compounds of this invention.

Davidsen is cited for teaching "that pyridine salts are known to be extremely soluble." Davidsen does not teach this. All Davidsen teaches is that the pyridine containing compound 4 is improved in respect to it's water solubility through the formation of certain salts disclosed in Table 1. These pyridinium compounds are no way related to the compounds of this invention, except that they contain a pyridine ring within their structure. Unlike Hayase or Hudyama, the compounds of Davidsen contain no triazole of Part B within their structure. In addition, the compounds of Davidsen are used for an entirely different purpose than the compounds of this invention and the compounds of Hayase or Hudyama. No basis exists for incorporating a pyridine moiety in the Hudyama and Hayase structures. Furthermore, even with such an incorporation, one would still not produce the claimed compounds of this invention. Davidsen does

not suggest incorporating a pyridine moiety in compounds having the structures of Hudyama or Hayase.

Without such a suggestion of incorporating a pyridine moiety in compounds having the structures of Hudyama or Hayase, there can be no rejection on obviousness. Attention is directed to In re Gordon, 221 USPQ 115 (CAFC 1984) where the rejected claims were directed to the prior apparatus turned upside down. In holding the claimed invention patentable since there was no teaching of turning the apparatus upside down, the CAFC stated:

> "The question is not whether a patentable distinction is created by viewing prior at apparatus from one direction and a claimed apparatus from another, but, rather, whether it would have been obvious from a fair reading of the prior art reference as a whole to turn the prior art apparatus upside down .... The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of such a modification." (221 UPSQ 1125, 1127)

The suggestion, even a simple one of turning the apparatus upside down, must come from the prior art and not from the examiner.

3. No Basis Exists For Combining the References

No basis is asserted for this combination except that Hayase and Hudyama all disclose fungicidal active compounds. On the other hand, this combination is not complete unless the pyridine disclosed by Davidsen is incorporated into the combination with Hayase. Even with this incorporation, the compounds of this invention would not be formed. No basis exsists for incorporating Davidsen's pyridine into Hayase's or Hudyama's since Davidsen's compounds are totally different in structure and utility from the compounds of either Hayase or Hudyama.

To combine references on the basis that one could substitute the material of one reference for a different material disclosed in another reference as a design choice is not sufficient for an obviousness rejection unless there is also suggestion in the art to make

this substitution with the expectation that success would result. In In re Vaeck, 20 USPQ2d 1438 (CAFC 1991), the invention was a chimeric gene composed of a cyanobacter promoter fused to a Bacillus gene encoding an insecticidal protein. The rejection was based on prior art disclosing cyanobacter promoters fused to other genes, and prior art disclosing the Bacillus insecticidal protein gene expressed in other heterologous hosts. In holding that this was an improper combination and rejection, the CAFC stated

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under §103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the art process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success ... [citation omitted] ... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." 20 USPQ2d 1438 at 1442.

Thus for an obviousness rejection, the references must provide more than a design choice or an obvious method by which a claimed product may be obtained. The references must go further, to provide both a suggestion to combine the disclosures of the references to obtain the claimed product, and a reasonable expectation that such a combination of disclosures would successfully yield the claimed product having its desirable properties (see also Ex parte Obukowicz, 27 USPQ2d 1063 (BPAI 1993). No basis exists for making this combination.

No evidence or proof has been provided to support a conclusion that obviousness modifications would result in a compound having the claimed properties. Therefore, the rejection improperly deems applicants' claimed invention obvious. Reliance upon applicants' disclosure and that some of the materials used to formulate the claimed compounds are known cannot be used to provide the requisite evidence of obviousness. There is no teaching in any of the references of any compound embodying the claimed

construction of Part A and Part B or that by combining Part B with Part A in the claimed manner to produce the claimed compound having greater therapeutic value than the compound of Part B.

4. The Umeda Declaration

While Applicants respectfully submit that the above arguments clearly render the present claims neither anticipated nor obvious over Hayase, Applicants have gone further by previously supplying a declaration of Isao Umeda. The Umeda declaration shows that the antigenicity of the N-substituted carbamoyloxyalkyl-azolium derivatives of the present invention is negative while the antigenicity of the corresponding compounds of the Hayase is positive. This declaration presents evidence that demonstrates that the claimed compound consisting of Parts A and B has different properties than the compound of Hayase which contains the triazole of Part B.

Dr. Umeda's Declaration is submitted to demonstrate that all compounds derived the triazole of Part B do not have the same properties. This Declaration is not submitted to provide comparative evidence between the prior art compound and the compounds of this invention. It appears that the closest prior art compound is the triazole of Part B or the precursor disclosed by the Hayase et al. patent. The Examiner is holding that the Hayase compound and the compounds formed from the Hayase compound are the same compounds. Clearly, as seen from the Declaration, this is not the case, they have different properties. To hold that a compound and the intermediate from which it is formed are the same compounds has no basis in law or in fact. No reason is given as to why the precursor and the final product are the same products and the precursor inherently anticipates the final product. As seen from the Declaration, this is not the case.

C. *The Use of Hydrolizable Aryl Groups in the Claims Satisfies 35 U.S.C. §112, First Paragraph, as to the Description and Enablement Requirements*

The term "hydrolizable acyl radical" is specifically described in the specification. Please note page 5, lines 11-21, where the aryl moiety is used to designate acid radicals, which, as stated on lines 9 and 10 of page 5, are easily hydrolized under physiological conditions.

The instant specification defines that any acyl radicals which is hydrolyzable can be used in accordance with this invention. These hydrolyzable acyl radicals, as set forth in this application, do not form the novel part of this invention but are used to protect free amino and hydroxyl groups by forming amides or esters. The use of hydrolyzable acyl protecting groups is not novel and is well known in the art and clearly the term hydrolyzable acyl radical defines a well known class of radicals used for this purpose. This is sufficient to meet the requirements of 35 U.S.C. §112, first paragraph.

Attention is directed to In re Robins, 166 USPQ 552 (CCPA 1970), which reversed a rejection of a claim under 35 U.S.C. §112, first paragraph, for lack of support. The CCPA held that 35 U.S.C. §112, first paragraph, is satisfied if the claims are as broad as the statements in the applicants' specification:

> "If the examiner and/or the board intended a rejection under the first paragraph of §112, it must be reversed inasmuch as the specification contains a statement of appellant's invention which is as broad as appellant's broadest claims..." 162 USPQ 552, at 555

This invention is directed to compounds. It is these compounds which are the novel part of this invention, not the ester or amide form of this compound produced by means of hydrolizable acyl radicals. Consequently, applicants disclosure is commensurate in scope with the claims and meets the requirements of 35 U.S.C. §112, first paragraph.

In the Final Office Action, In re Sus, 134 USPQ 301 and In re Cavallito, are relied upon for demonstrating that the term "hydrolizable acyl" is too broad. Neither the Sus nor Cavallito cases, *supra*, support this conclusion. The use of the term "acyl" in these cases was not set forth in the specification. In addition, the specification in these cases did not indicate that all such acyl radicals were usable in accordance with their invention. As stated by the CCPA, In re Robbins, *supra*, in holding that the term "monoorgano" in the claims met the requirements of 35 U.S.C. §112, first paragraph:

> "In Sus, appellant used the terms "aryl and substituted aryl radicals" or "substituted and unsubstituted aryl radicals" in his claims. However, we found nothing in the way of express statements *or examples* in the specification that would teach one skilled in the art that "all 'aryl and substituted aryl radicals' were properly within the subject matter which appellants considered to be their invention." Accordingly we held that the claims were broader than the disclosure. 166 USPQ 552, 557-558

In this regard, also see note 4 of the Robbins *supra* opinion. In the present case there are express statements of appellant's invention which are as broad as his claims. Therefore, In re Sus, *supra*, is not in point." In the instant application, as seen from page 5, any hydrolized acyl moiety can be used in accordance with this invention. Therefore, the specification states that such an acyl moiety can be used in accordance with this invention and this complies with the requirements of 35 U.S.C. §112.

That a term such as "acyl defines a well defined class of radicals known to one skill in the art has been recognized continually in cases by the board and courts which have held that the use of this term in a claim, where they do not define the point of novelty, is in accordance with the requirements of 35 U.S.C. 112, first and second paragraph. As stated by the Board of Appeals in Ex parte Scherberich, 201 U.S.P.Q. 397, in reversing a rejection of the claims under 35 U.S.C. 112 first and second paragraphs, for using terms such as "aryl" and "aralkyl":

> "As to the term 'aryl, it is recognized that various authorities may place a slightly different interpretation on its meaning; ...we are of the opinion that those in the art readily appreciate the total scope of the subject matter being defined. Irrespective of whether the term 'aryl' is restricted to an 'organic radical derived from an aromatic hydrocarbon by the removal of one atom; e.g., phenyl from benzene, or could be read as inclusive of the tolyl radical...it is believed apparent that the claims' use of the three terms 'aryl', 'aralkyl' and 'aralkyl' clearly indicates the intended scope of the substituent groups'." 201 U.S.P.Q. 397, 399

The term "acyl" like the term aryl as set forth in Ex parte Scherberich, supra, clearly indicates the intended scope of the substituent groups. The novelty of Applicants' invention does not reside in the hydrolyzable acyl radicals since such are known in the art. Therefore, this term meets the requirements of 35 U.S.C. §112. That the term acyl covers a myriad of substituents is not ground for a rejection under 35 U.S.C. §112 Based upon the foregoing, it is submitted that the term "acyl" as used in the claims is in accordance with 35 U.S.C. §112, first and second paragraph.

In the aforementioned Office Action, In re Kirk et al, 153 USPQ 48 (CCPA 1967) is cited as a basis for holding that the use of broads terms do not satisfy the written description or enablement requirements of 35 U.S.C. §112 The decision of the CCPA in In re Kirk, supra, has nothing to do with any issue concerning the written description or enablement requirements of 35 U.S.C. §112 but rather with the adequacy of the Utility statement in the Kirk application In the Kirk case, the involved application disclosed that the claimed compound was a steroid and it possessed "biological activity In holding that this was an inadequate disclosure of utility and therefore the application failed to comply with 35 U.S.C. §101 and 112 ,the CCPA ,in the Kirk case, *supra*, stated on page 49:

> The Patent Office rejected all the claims for failure of the "specification to comply with 35 U.S.C. §101 and 112". As we review the record, we are concerned with not only the legal adequacy of appellants' disclosure of "how to use" the claim

> invention under 35 U.S.C. §112 but also the legal adequacy of the assertions of usefulness in the original specification under 35 U.S.C. §101.

It can not be seen how the Kirk case is applicable to whether the tem aryl defines the substituents to one skilled in the art. There is no rejection on the legal adequacy of the utility disclosure with regard to the instant compounds. In the Kirk case, the CCPA found that "biological activity" did not define any utility to one skilled in the art. Certainly, this is not the case in the instant application and the use of the term such as aryl and acyl do define the substitutions encompassed by these terms to one skilled in the art. This is clearly stated in the Ex parte Scherberich, *supra* and the In re Robbins, *supra* decisions.

That the term "acyl" encompasses a myriad of different groups, does it in fur burden on one skilled in the art is. The term "acyl" defines a well known class of radicals, the members of which can be determined by one skilled in the art. See In re Fuetterer, 138 USPQ 217 (CCPA 1963), wherein the CCPA reversed a rejection where applicant claimed his invention as utilizing any inorganic salt capable of performing a specific function in a specific combination while only disclosing four such salts, stating:

> "We find the arguments of the board and the examiner relating to experimentation necessary to determine the suitability of undisclosed salts to operate in appellant's claimed combination beside the point. Appellant's invention is the combination claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination."138 USPQ 217, at 223.

With respect to this burden, one skilled in the art, the CCPA stated in In re Fuetterer:

> "The only "undue burden" which is apparent to us in the instant case is that which the Patent Office has attempted to place on the appellant. The

Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented, and is not claiming colloid suspending agents but tire tread stock composed of a combination of rubber and other ingredients."

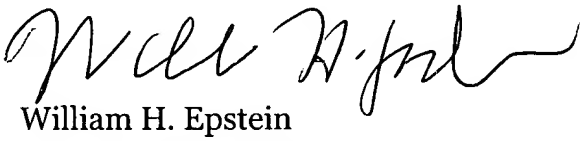
XIII. CONCLUSION

Claims 1-9, 15-18, 22-23, 26-27 and 30-31 are not anticipated under 35 U.S.C. §102(e) by Hayase or rendered obvious under 35 U.S.C. §103 by Hayase in view of Hudyama and Davidsen.

Claims 3 and 4 comply with the requirements of 35 U.S.C. §112, first paragraph.

This Brief is provided in triplicate.

Respectfully submitted,



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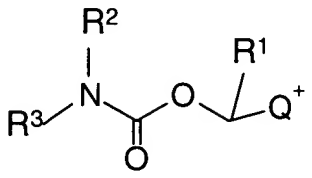
Appendix A

1. A compound of the formula (I),



X- (I)

wherein

Q is a 3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol moiety which is linked to the remainder of the compound of formula (I) by a nitrogen in the triazole;

R_1 is hydrogen or alkyl;

R_2 is hydrogen, alkyl, alkylcarbonyloxyalkyl, alkoxycarbonyl, alkylcarbonyl, mono- or dialkylaminoalkylcarbonyloxyalkyl;

R_3 is pyridin-2-yl or substituted pyridin-2-yl; and

X^- is a pharmaceutically acceptable anion,

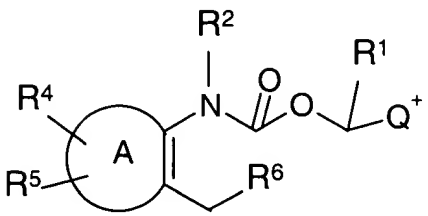
wherein

when R_3 is substituted pyridin-2-yl, the substituent is selected from the group consisting of halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkyloxycarbonyl, cyano, trifluoromethyl, trifluoromethoxy, nitro, aminosulfonyl, alkylaminocarboyloxyalkyl, sulfo, alkylcarbonyloxyalkyl and aminoalkylcarbonyloxyalkyl;

or a pharmaceutically acceptable salt thereof.

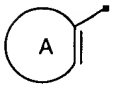
2. The compound of claim 1 wherein R_3 is substituted pyridin-2-yl.

3. The Compound of claim 2 having formula (II),



X^- (II)

wherein

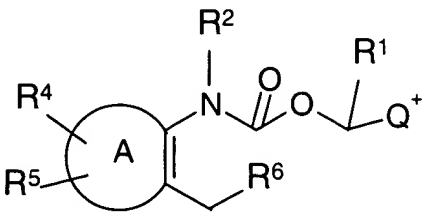


is pyridin-2-yl;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkyloxycarbonyl, cyano, trifluoromethyl, trifluoromethoxy nitro, aminosulfonyl, alkylaminocarboyloxyalkyl, sulfo, alkylcarbonyloxyalkyl and aminoalkylcarbonyloxyalkyl; and

R^6 is hydroxy, alkoxycarbonylalkylamino, alkoxycarbonylamino, amino, alkylamino, alkylcarbonyloxy, alkoxycarbonylalkylaminoalkylcarbonyloxy, alkoxycarbonylamino-alkylcarbonyloxy, alkylaminoalkylcarbonyloxy, aminoalkylcarbonyloxy, alkylcarbonylamino, alkylcarbonylalkylamino, acyloxy, acylamino, acylalkylamino wherein said acyl group is a hydrolizable radical.

4. Compounds of claim 3 having formula (III),



X^- (III)

wherein

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkyloxycarbonyl, cyano, trifluoromethyl, trifluoromethoxy, nitro, aminosulfonyl or sulfo; and

R^6 is hydroxy, alkoxycarbonylalkylamino, alkoxycarbonylamino, amino, alkylamino, alkylcarbonyloxy, alkoxycarbonylalkylaminoalkylcarbonyloxy, alkoxycarbonylamino-alkylcarbonyloxy, alkylaminoalkylcarbonyloxy, aminoalkylcarbonyloxy, alkylcarbonylamino, alkylcarbonylalkylamino, acyloxy, acylamino, acylalkylamino wherein said acyl is a hydrolizable radical.

5. The compound of claim 4 wherein R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, alkoxy, cyano, trifluoromethyl, trifluoromethoxy and nitro.

6. The compound of claim 5 wherein R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen and alkoxy.

7. The compound of claim 4 wherein R^4 and R^5 are hydrogen.

8. The compound of claim 4 wherein R^6 is alkylamino, alkylcarbonyloxy, alkylaminoalkylcarbonyloxy or aminoalkylcarbonyloxy.

9. The compound of claim 8 wherein R^6 is alkylaminoalkylcarbonyloxy.

15. The compound of claim 1 wherein R^1 is hydrogen or alkyl.

16. The compound of claim 15 wherein R^1 is methyl.

17. The compound of claim 1 wherein R^2 is hydrogen or alkyl.

18. The compound of claim 17 wherein R^2 is alkyl.

22. The compound of claim 1 wherein X is a halogen.

23. The compound of claim 22 wherein X is chloro.

26. A compound selected from the group consisting of

1-[[N-methyl-N-3-[(methylamino)acetoxymethyl]pyridin-2-yl]carbamoyloxy]ethyl-1-[(2R,3R)-2-(2,5-difluorophenyl)-2-hydroxy-3-[4-(4-cyanophenyl)thiazol-2-yl]butyl]-1H-[1,2,4]triazol-4-ium chloride dihydrochloride,

1-[[N-methyl-N-3-[(methylamino)acetoxymethyl]pyridin-2-yl]carbamoyloxy]ethyl-1-[(2R,3R)-2-(2,5-difluorophenyl)-2-hydroxy-3-[4-(4-cyanophenyl)thiazol-2-yl]butyl]-1H-[1,2,4]triazol-4-ium chloride hydrochloride, or

1-[[N-methyl-N-3-(acetoxymethyl)pyridin-2-yl]carbamoyloxy]ethyl-1-[(2R,3R)-2-(2,5-difluorophenyl)-2-hydroxy-3-[4-(4-cyanophenyl)thiazol-2-yl]butyl]-1H-[1,2,4]triazol-4-ium chloride hydrochloride,

27. A compound which is 1-[[N-methyl-N-3-[(methylamino)acetoxymethyl]pyridin-2-yl]carbamoyloxy]ethyl-1-[(2R,3R)-2-(2,5-difluorophenyl)-2-hydroxy-3-[4-(4-cyanophenyl)thiazol-2-yl]butyl]-1H-[1,2,4]triazol-4-ium chloride hydrochloride.

30. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

31. A method of treating fungal infections comprising administering to the infected organism an effective amount of a compound of claim 1.